

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
21 April 2005 (21.04.2005)

PCT

(10) International Publication Number
WO 2005/035530 A1

(51) International Patent Classification⁷: **C07D 413/10**

(21) International Application Number:
PCT/IN2003/000336

(22) International Filing Date: 16 October 2003 (16.10.2003)

(25) Filing Language: English

(26) Publication Language: English

(71) Applicant (for all designated States except US): **SYMED LABS LIMITED** [IN/IN]; 8-3-166/6 & 7, II Floor, Sree Arcade, Erragadda, Hyderabad 500 018, Andhrapradesh (IN).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **MOHAN RAO, Dodda** [IN/IN]; Symed Labs Limited, 8-3-166/6 & 7, II Floor, Sree Arcade, Erragadda, Hyderabad 500 018, Andhrapradesh (IN). **KRISHNA REDDY, Pingili** [IN/IN]; Symed Labs Limited, 8-3-166/6 & 7, II Floor, Sree Arcade, Erragadda, Hyderabad 500 018, Andhrapradesh (IN).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)
- of inventorship (Rule 4.17(iv)) for US only

Published:

- with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2005/035530 A1

(54) Title: A NOVEL CRYSTALLINE FORM OF LINEZOLID

(57) Abstract: The present invention relates to a novel crystalline form of linezolid, to processes for its preparation and to a pharmaceutical composition containing it.

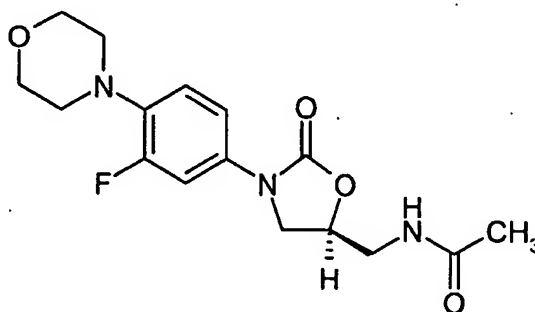
A NOVEL CRYSTALLINE FORM OF LINEZOLID

FIELD OF THE INVENTION

5 The present invention relates to a novel crystalline form of linezolid, to processes for its preparation and to a pharmaceutical composition containing it.

BACKGROUND OF THE INVENTION

10 Linezolid, chemically N-[[[(5S)-3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide is an antibacterial agent. Linezolid is represented by the following structure:



15 Linezolid and related compounds, processes for their preparation and their therapeutic uses were disclosed in US 5,688,792. Processes for preparation of linezolid were also described in US 5,837,870, WO 99/24393, J.Med.Chem. 39(3), 673-679, 1996 and Tetrahedron Lett., 40(26), 4855, 1999.

20 Linezolid is known to exhibit polymorphism and two crystalline forms are so far known. US 6,559,305 and US 6,444,813 addressed that the product obtained by the process described by J.Med.Chem. 39(3), 673-679, 1996 is form I and is characterized by having melting point of 181.5-182.5°C and by IR spectrum having bands at 3284, 3092, 1753, 1728, 1649, 1565, 1519, 1447, 1435 cm⁻¹. US 6,559,305 claims crystalline form II characterized by IR spectrum having bands at 3364, 1748, 1675, 1537, 1517, 1445, 1410, 1401, 1358, 1329, 25 1287, 1274, 1253, 1237, 1221, 1145, 1130, 1123, 1116, 1078, 1066, 1049, 907, 852 and 758 cm⁻¹ and powder X-ray diffraction spectrum having 2-theta values

at 7.10, 9.54, 13.88, 14.23, 16.18, 16.79, 17.69, 19.41, 19.69, 19.93, 21.61, 22.39, 22.84, 23.52, 24.16, 25.28, 26.66, 27.01 and 27.77 degrees.

We have discovered a novel crystalline form (form III) of linezolid. The novel crystalline form of linezolid is consistently reproducible, does not have the tendency to convert to other forms and found to be thermally more stable than form I or form II. Furthermore, form III bulk solid is more compact and less electrostatic than form II and hence is more readily subjected to any treatment under the usual conditions of the pharmaceutical technology, in particular, of formulation on an industrial scale. Therapeutic uses of linezolid were disclosed in US 5,688,792.

The object of the present invention is to provide a stable, consistently reproducible crystalline form of linezolid; processes for preparing it; and a pharmaceutical composition containing it.

SUMMARY OF THE INVENTION

In accordance with the present invention, there is provided a novel crystalline form of linezolid, designated as linezolid form III.

Linezolid form III is characterized by peaks in the powder x-ray diffraction spectrum having 2θ angle positions at about 7.6, 9.6, 13.6, 14.9, 18.2, 18.9, 21.2, 22.3, 25.6, 26.9, 27.9 and 29.9 degrees.

Linezolid form III is further characterized by IR spectrum having main bands at about 3338, 1741, 1662, 1544, 1517, 1471, 1452, 1425, 1400, 1381, 1334, 1273, 1255, 1228, 1213, 1197, 1176, 1116, 1082, 1051, 937, 923, 904, 869, 825 and 756 cm^{-1} .

Linezolid form III is obtained by heating linezolid in a known crystalline form or in a mixture of known crystalline forms until the known form/s are converted to form III.

The known form may be heated directly to obtain linezolid form III; or linezolid form III may be obtained by heating linezolid suspended in a solvent like toluene, xylene, etc.

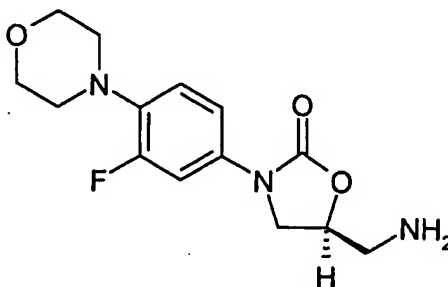
The conversion to form III occurs at above about 90°C , preferably between 100°C and 200°C and more preferably between 120°C and 140°C .

The heating takes at least about 30 min, usually about 2 hours to 12 hours and typically about 4 hours to 10 hours.

In accordance with the present invention, an alternative process is provided for preparation of linezolid form III, which comprises the steps of:

- a) acetylating (S)-N-[[3-[3-fluoro-4-[4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]amine of formula

5



in a solvent optionally in the presence of an organic base to form linezolid;

b) optionally seeding the reaction mixture formed in step (a); and

c) isolating linezolid form III from the reaction mixture of (a) or (b);

- 10 wherein the solvent is selected from the group consisting of ethylacetate, methylacetate, propylacetate, isopropylacetate, butylacetate, acetonitrile, chloroform, methylenedichloride, benzene, toluene and xylene.

The organic base is preferably selected from pyridine; tri(C1-C4)alkylamine e.g. triethylamine and N,N-diisopropyl ethylamine; and N,N-
15 di(C1-C3)alkylaniline e.g. N,N-dimethylaniline.

In accordance with the present invention, still another process is provided for preparation of linezolid form III, which comprises the steps of:

a) mixing linezolid with a solvent or a mixture of solvents;

b) cooling the contents to below about 15°C;

- 20 c) optionally seeding the contents with linezolid form III;

d) stirring the contents for at least about 15 min; and

e) collecting linezolid form III crystals by filtration or centrifugation;

wherein the solvent is selected from the group consisting of toluene, xylene, chloroform methylene dichloride, acetonitrile, water, R₁-OH, R₁-CO-R₂, R₁-CO-

- 25 O-R₂, R₁-O-R₂ wherein R₁ and R₂ are independently C₁-C₆ alkyl groups. Preferable solvents are toluene, xylene, chloroform, methylene dichloride, acetonitrile, water, methanol, ethanol, propanol, isopropyl alcohol, tert-butyl

alcohol, acetone, methyl ethyl ketone, ethylacetate, diethyl ether and methyl tert-butyl ether. Most preferable solvents are isopropyl alcohol and ethylacetate.

In accordance with the present invention, there is provided a pharmaceutical composition comprising linezolid form III and a pharmaceutically acceptable carrier or diluent.

DETAILED DESCRIPTION OF THE INVENTION

In accordance with the present invention, there is provided a novel crystalline form of linezolid, designated as linezolid form III.

Linezolid form III is characterized by peaks in the powder x-ray diffraction spectrum having 2θ angle positions at about 7.6, 9.6, 13.6, 14.9, 18.2, 18.9, 21.2, 22.3, 25.6, 26.9, 27.9 and 29.9 degrees.

Linezolid form III is further characterized by IR spectrum having main bands at about 3338, 1741, 1662, 1544, 1517, 1471, 1452, 1425, 1400, 1381, 1334, 1273, 1255, 1228, 1213, 1197, 1176, 1116, 1082, 1051, 937, 923, 904, 869, 825 and 756 cm^{-1} .

Linezolid form III is obtained by heating linezolid in a known crystalline form or in a mixture of known crystalline forms until the known form/s are converted to form III.

The known form may be heated directly to obtain linezolid form III; or linezolid form III may be obtained by heating linezolid suspended in a solvent like toluene, xylene, etc.

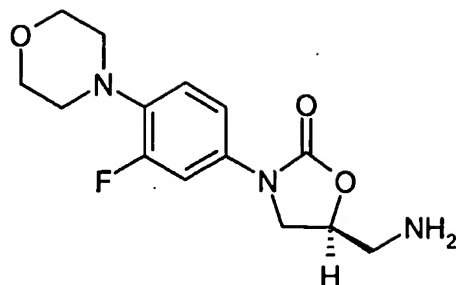
The conversion to form III occurs at above about 90°C , preferably between 100°C and 200°C and more preferably between 120°C and 140°C .

The heating takes at least about 30 min, usually about 2 hours to 12 hours and typically about 4 hours to 10 hours.

No racemization occurs during the heating of linezolid as evidenced by enantiomeric purity, which is same before and after heating.

In accordance with the present invention, an alternative process is provided for preparation of linezolid form III.

Thus, (S)-N-[[3-[3-fluoro-4-[4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]amine of formula



is reacted with an acetylating agent, like acetic anhydride, acetyl chloride, in a solvent optionally in the presence of an organic base and linezolid
5 formed is isolated from the reaction mixture.

The solvent is selected from the group consisting of ethylacetate, methylacetate, propylacetate, isopropylacetate, butylacetate, acetonitrile, chloroform, methylenedichloride, benzene, toluene and xylene.

The organic base is preferably selected from pyridine; tri(C1-
10 C4)alkylamine e.g. triethylamine and N,N-diisopropyl ethylamine; and N,N-di(C1-C3)alkylaniline e.g. N,N-dimethylaniline.

Preferably, (S)-N-[[3-[3-fluoro-4-[4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]amine is mixed in ethyl acetate, acetic anhydride is added
15 maintaining the reaction temperature at or below boiling temperature of ethylacetate, preferably at about 15°C to 40°C; the reaction mixture is agitated preferably at about 15°C to 40°C for at least 15 min; and linezolid form III is collected by filtration or centrifugation.

The reaction mixture is optionally seeded with linezolid form III before isolating linezolid form III.

20 In accordance with the present invention, still another process is provided for preparation of linezolid form III.

Thus, linezolid is mixed with a solvent. Linezolid is preferably mixed at boiling point of the solvent used. The solvent is selected from the group consisting of toluene, xylene, chloroform methylene dichloride, acetonitrile,
25 water, R₁-OH, R₁-CO-R₂, R₁-CO-O-R₂, R₁-O-R₂ wherein R₁ and R₂ are independently C₁-C₆ alkyl groups. Preferable solvents being toluene, xylene, chloroform, methylene dichloride, acetonitrile, water, methanol, ethanol, propanol, isopropyl alcohol, tert-butyl alcohol, acetone, methyl ethyl ketone,

ethylacetate, diethyl ether and methyl tert-butyl ether. Most preferable solvents being isopropyl alcohol and ethylacetate. A mixture of solvents may also be used and solvents like hexane, heptane may also be added in order to enhance crystallization in latter stages. Linezolid obtained by a known method is used in the process.

The solution obtained as above is cooled to below about 15°C, preferably to about 0°C to about 15°C, more preferably to about 0°C to about 10°C.

The contents are optionally seeded with linezolid form III.

The contents are then stirred for at least about 15 min, preferably for about 30 min to 8 hours and more preferably about 1 hour to about 5 hours.

Linezolid form III crystals are then collected by filtration or centrifugation.

In accordance with the present invention, there is provided a pharmaceutical composition comprising linezolid form III and a pharmaceutically acceptable carrier or diluent.

The invention will now be further described by the following examples; which are illustrative rather than limiting.

Example 1

Linezolid (10 gm, obtained by the process described in US 5,688,792 Example 5) is heated at 130°C to 140°C under N₂ atmosphere for 4 hours to give linezolid form III quantitatively.

Example 2

Linezolid form II (10 gm, with 99.8% ee) is suspended in toluene (50 ml) and refluxed for 3 hours. the contents are cooled to 25°C and filtered to obtain 9.8 gm of linezolid form III (99.8% ee).

Example 3

Linezolid (10 gm, obtained by the process described in US 5,688,792 Example 5) is mixed with isopropyl alcohol (200 ml), heated to 80°C and stirred for 10 min at the same temperature to form a clear solution. The solution is cooled to 0°C, stirred for 1 hour 30 min at 0°C and filtered to give 9.7 gm of linezolid form III

Example 4

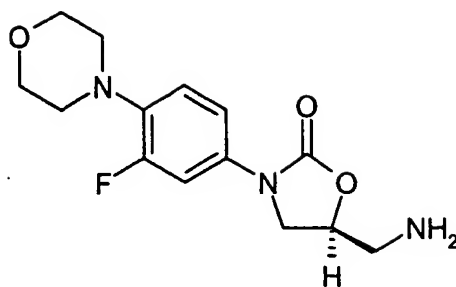
Example 3 is repeated by seeding the solution with linezolid form III during maintenance at about 0°C. Yield of linezolid form III is 9.6 gm.

Example 5

To the mixture of (S)-N-[[3-[3-fluoro-4-[4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]amine (10 gm) and ethylacetate (100 ml), acetic anhydride (10 ml) is slowly added at ambient temperature, then stirred at ambient
5 temperature for 1 hour. The separated solid is filtered and dried under reduced pressure at 50°C to give 9.5 gm of linezolid form III.

We claim:

1. A crystalline linezolid form III, characterized by an x-ray powder diffraction spectrum having peaks expressed as 2θ at about 7.6, 9.6, 13.6, 14.9, 18.2, 18.9, 21.2, 22.3, 25.6, 26.9, 27.9 and 29.9 degrees.
- 5 2. A crystalline linezolid form III as defined in claim 1, further characterized by by IR spectrum having main bands at about 3338, 1741, 1662, 1544, 1517, 1471, 1452, 1425, 1400, 1381, 1334, 1273, 1255, 1228, 1213, 1197, 1176, 1116, 1082, 1051, 937, 923, 904, 869, 825 and 756 cm^{-1} .
- 10 3. A process for preparation of linezolid form III as defined in claim 1, which comprises the step of heating linezolid in a known crystalline form or in a mixture of known crystalline forms until the known form/s are converted to form III.
4. A process according to claim 3, wherein linezolid is heated directly or linezolid suspended in a solvent is heated.
- 15 5. A process according to claim 4, wherein linezolid is heated at above about 90°C for at least 30 min.
6. A process according to claim 5, wherein linezolid is heated between 100°C and 200°C for about 2 hours to 12 hours.
7. A process according to claim 6, wherein linezolid is heated between 120°C and 140°C for about 4 hours to 10 hours.
- 20 8. A process according to claim 4, wherein linezolid suspended in toluene is heated at about boiling temperature of the solvent for about 4 hours to 10 hours.
9. A process according to claim 4, wherein linezolid suspended in xylene is heated at about boiling temperature of the solvent for about 4 hours to 10 hours.
- 25 10. A process for preparation of linezolid form III as defined in claim 1, which comprises the steps of:
 - a) acetylating (S)-N-[[3-[3-fluoro-4-[4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]amine of formula in a solvent
- 30



optionally in the presence of an organic base to form linezolid;

b) optionally seeding the reaction mixture formed in step (a); and

5 c) isolating linezolid form III from the reaction mixture of (a) or (b);

wherein the solvent is selected from the group consisting of ethylacetate, methylacetate, propylacetate, isopropylacetate, butylacetate, acetonitrile, chloroform, methylenedichloride, benzene, toluene and xylene.

10 11. A process according to claim 10, wherein the process is carried out in the presence of the organic base.

12. A process according to claim 10, wherein the organic base is selected from pyridine, tri(C1-C4)alkylamine and N,N-di(C1-C3)alkylaniline.

13. A process according to claim 12, wherein the organic base is pyridine, triethylamine, N,N-diisopropyl ethylamine and N,N-dimethylaniline.

15 14. A process according to claim 10, wherein the process is carried out in the absence of the organic base.

15. A process according to claim 10-14, wherein the solvent is ethylacetate.

16. A process according to claim 10-15, wherein linezolid form III is isolated without seeding.

20 17. A process according to claim 10-15, wherein linezolid form III is isolated after seeding.

18. A process for preparation of linezolid form III as defined in claim 1, which comprises the steps of:

a) mixing linezolid with a solvent or a mixture of solvents;

25 b) cooling the contents to below about 15°C;

c) optionally seeding the contents with linezolid form III;

d) stirring the contents for at least about 15 min; and

e) collecting linezolid form III crystals by filtration or centrifugation;
wherein the solvent is selected from the group consisting of toluene, xylene, chloroform methylene dichloride, acetonitrile, water, R_1 -OH, R_1 -CO- R_2 , R_1 -CO-O- R_2 and R_1 -O- R_2 where R_1 and R_2 are independently C_1 to C_2 alkyl groups.

- 5 19. A process according to claim 18, wherein the solvent is selected from toluene, xylene, chloroform, methylene dichloride, acetonitrile, water, methanol, ethanol, propanol, isopropyl alcohol, tert-butyl alcohol, acetone, methyl ethyl ketone, ethylacetate, diethyl ether and methyl tert-butyl ether.
- 10 20. A process according to claim 19, wherein the solvent is isopropyl alcohol or ethyl acetate.
21. A process according to claim 20, wherein the solvent is isopropyl alcohol.
22. A process according to claim 20, wherein the solvent is ethyl acetate.
23. A process according to claim 18, wherein the contents in step (b) is cooled to 0°C to 10°C and stirring the contents in step (d) for about 30 min to 8
- 15 hours;
24. A pharmaceutical composition comprising linezolid form III of claim 1 and a pharmaceutically acceptable carrier or diluent.